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(21) International Application Number: PCT/DK99/00681 (22) International Filing Date: 3 December 1999 (03.12.99) (30) Priority Data: PA 1998 01610 4 December 1998 (04.12.98) DK (71) Applicant (for all designated States except US): NEUROSEARCH A/S [DK/DK]; Pederstrupvej 93, DK-2750 Ballerup (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): TEUBER, Lene [DK/DK]; NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). CHRISTOPHERSEN, Palle [DK/DK]; NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). STRØBÆK, Dorte [DK/DK]; NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). JENSEN, Bo, Skaaning [DK/DK]; NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK). (74) Common Representative: NEUROSEARCH A/S; Patent Department, Pederstrupvej 93, DK-2750 Ballerup (DK).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NEW BENZIMIDAZOLONE-, BENZOXAZOLONE-, OR BENZOTHIAZOLONE DERIVATIVES AS ION CHANNEL MODULATING AGENTS (57) Abstract The present invention relates to ion channel modulating agents. More particularly, the present invention relates to a particular class of chemical compounds that has proven useful as modulators of SK _{Ca} , IK _{Ca} and BK _{Ca} channels. In further aspects, the present invention relates to the use of these SK/IK/BK channel modulating agents for the manufacture of medicaments, and pharmaceutical compositions comprising the SK/IK/BK channel modulating agents. The SK/IK/BK channel modulating agents of the invention are useful for the treatment or alleviation of diseases and conditions associated with the SK/IK/BK channels.		

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NEW BENZIMIDAZOLONE-, BENZOXAZOLONE-, OR BENZOTHAZOLONE DERIVATIVES AS ION CHANNEL MODULATING AGENTS

TECHNICAL FIELD

5 The present invention relates to ion channel modulating agents. More particularly, the present invention relates to a particular class of chemical compounds that has proven useful as modulators of SK_{Ca}, IK_{Ca} and BK_{Ca} channels. In further aspects, the present invention relates to the use of these SK/IK/BK channel modulating agents for the manufacture of medicaments, and pharmaceutical
10 compositions comprising the SK/IK/BK channel modulating agents.

The SK/IK/BK channel modulating agents of the invention are useful for the treatment or alleviation of diseases and conditions associated with the SK/IK/BK channels.

15

BACKGROUND ART

Ion channels are transmembrane proteins, which catalyse the transport of inorganic ions across cell membranes. The ion channels participate in processes as diverse as the generation and timing of action potentials, synaptic transmissions,
20 secretion of hormones, contraction of muscles, etc.

Many drugs exert their effects via modulation of ion channels. Examples are anti-epileptic compounds like Phenytoin and Lamotrigine, which block voltage dependent Na⁺-channels in the brain, anti-hypertensive drugs like Nifedipine and Diltiazem, which block voltage dependent Ca²⁺-channels in smooth muscle cells, and
25 stimulators of insulin release like Glibenclamide and Tolbutamide, which block an ATP-regulated K⁺-channel in the pancreas.

All mammalian cells express potassium (K⁺) channels in their cell membranes, and the channels play a dominant role in the regulation of the membrane potential. In nerve and muscle cells they regulate the frequency and form of the action
30 potential, the release of neurotransmitters, and the degree of broncho- and vasodilation.

From a molecular point of view, the K⁺ channels represent the largest and most diverse group of ion channels. For an overview they can be divided into five

large subfamilies: Voltage-activated K^+ channels (K_v), long QT related K^+ channels (K_vLQT), inward rectifiers (K_{IR}), two-pore K^+ channels (K_{TP}), and calcium-activated K^+ channels (K_{Ca}).

The latter group, the Ca^{2+} -activated K^+ channels, consists of three well-defined subtypes: SK channels, IK channels and BK channels. SK, IK and BK refer to the single-channel conductance (Small, Intermediate and Big conductance K channel). The SK, IK, and BK channels exhibit differences in e.g. voltage- and calcium-sensitivity, pharmacology, distribution and function.

Ca^{2+} -activated SK channels are present in many central neurons and ganglia, where their primary function is to hyperpolarize nerve cells following one or several action potentials to prevent long trains of epileptogenic activity to occur. The SK channels are also present in several peripheral cells including skeletal muscle, gland cells, liver cells, and T-lymphocytes.

The significance of SK channels in normal skeletal muscle is not clear, but their number is significantly increased in denervated muscle, and the large number of SK channels in the muscle of patients with myotonic muscle dystrophia suggest a role in the pathogenesis of the disease.

A number of blockers of SK channels exist, e.g. apamin, atracurium, pancuronium, and tubocurarine, and they are all positively charged molecules which act as pore blockers.

The Ca^{2+} -activated IK channel shares a number of characteristics with the Ca^{2+} -activated SK channel, since it is highly K-selective, is activated by sub-micromolar concentrations of Ca^{2+} , and has an inwardly rectifying conductance. However, there are also striking differences. The unit conductance of the IK channel is 4-5 fold higher than that of the SK channel, and the distribution of the IK channel is restricted to the blood and vasculature. Thus, the IK channel is not expressed in the nervous system and in muscle, but in endothelial cells, cells of epithelial origin and in red blood cells.

In the red blood cells, where the IK channel has been denominated the Gardos channel, a rise in the concentration of intracellular Ca^{2+} opens the channel and causes potassium loss and cell dehydration, a condition which is exacerbated in sickle cell anemia. Promising therapeutic approaches for sickle cell anemia involve specific block of the IK channel.

IK channels have also been implicated in the microvasculature of the kidney, where they may be responsible for the vasodilatory effects of bradykinin. The decrease in blood pressure during septic shock is caused by an increased NO production by the endothelial cells, and the IK channels in these cells are responsible
5 for maintaining the Ca^{2+} influx activating the Ca^{2+} -sensitive NO-synthase.

In brain capillary endothelial cells, IK channels, activated by endothelin that is produced by neurons and glia, shunt excess K^+ into the blood. Neurotrophic granulocytes, i.e. mobile phagocytic cells that defend the body against microbial invaders, undergo large depolarisation subsequent to agonistic stimulation, and IK
10 channels have been implicated in depolarising the stimulated granulocyte.

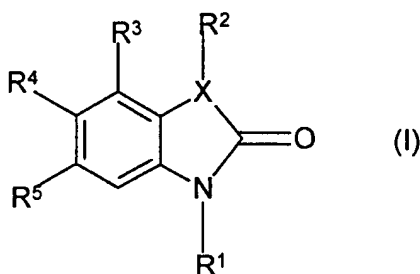
The Ca^{2+} -activated BK channels present in many cells including most central and peripheral nerve cells, striated muscle cells, cardiac cells, smooth muscle cells of the airways, the vasculature, the gastrointestinal tract and bladder, in endo- and exocrine glands including pancreatic b-cells and in kidney tubules.

15

SUMMARY OF THE INVENTION

According to the present invention it has now been found that a particular group of chemical compounds possess valuable activity as modulators of SK_{Ca} , IK_{Ca}
20 and/or BK_{Ca} channels.

In its first aspect the invention relates to novel chemical compounds represented by the general formula



25

wherein

X represents N, O, or S;

R^1 represents hydrogen; an alkyl group; a cycloalkyl group; hydroxy; an alkoxy group; an acyl group; a phenyl or a benzyl group, which phenyl and benzyl

groups may be substituted one or more times with substituents selected from halogen, -NO₂, -CN, -CF₃, alkyl, cycloalkyl, hydroxy, and alkoxy; a group of the formula -CH₂CN; a group of the formula -CH₂CO₂R', wherein R' represents hydrogen or an alkyl group; a group of the formula -CH₂CONR^{IV}R^V, wherein R^{IV} and R^V independently represents hydrogen or an alkyl group; or a group of the formula -CH₂C(=NOH)NH₂;

R² represents hydrogen, an alkyl group, a cycloalkyl group, a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, -NO₂, -CN, -CF₃, alkyl, cycloalkyl, hydroxy, and alkoxy; and

R³, R⁴ and R⁵ independently of each another represents hydrogen; halogen; -NO₂; -CN; -CF₃; an alkyl group; an alkoxy group; a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, -NO₂, -CN, -CF₃, alkyl, cycloalkyl, hydroxy, and alkoxy; or a group of the formula -SO₂NR''R''', wherein R'' and R''' independently of each another represents hydrogen or an alkyl group;

or R⁵ is as defined above and R³ and R⁴ together form an additional 4 to 7 membered fused ring, which fused ring may be aromatic or partially saturated, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halogen, -NO₂, -CN, -CF₃, or a group of the formula -SO₂NR''R''', wherein R'' and R''' independently of each another represents hydrogen or an alkyl group.

In a second aspect, the invention provides a pharmaceutical composition comprising a therapeutically-effective amount of the chemical compound of the invention, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for the treatment or alleviation of diseases or disorder or condition responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

In another aspect the invention relates to the use of a chemical compound of the invention for the manufacture of a pharmaceutical composition for the treatment or alleviation of a disorder or a disease or a condition of a mammal, including a human, which disorder, disease or condition is responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

In a final aspect the invention provides a method for the treatment or alleviation of disorders or diseases or conditions of a living animal body, including a human, which disorder, disease or conditions are responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound of the invention.

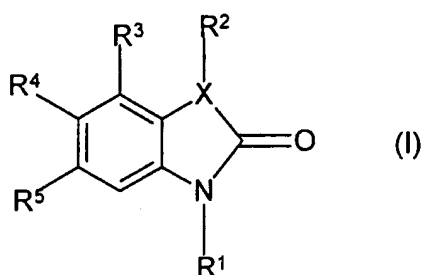
DETAILED DISCLOSURE OF THE INVENTION

According to the present invention it has now been found that a particular group of chemical compounds possess valuable activity as modulators of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

SK/IK/BK Modulating Agents

In the context of this invention, chemical compounds capable of affecting SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels are designated SK/IK/BK channel modulating agents. The SK/IK/BK channel modulating agents of the invention may affect the ion channels by opening (activating) the channels or by inhibiting (blocking) the channels.

The SK/IK/BK channel modulating agents of the invention belongs to a particular class of chemical compounds, represented by the general formula



wherein

X represents N, O, or S; and

R¹ represents hydrogen; an alkyl group; a cycloalkyl group; hydroxy; an alkoxy group; an acyl group; a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, -NO₂, -CN, -CF₃, alkyl, cycloalkyl, hydroxy, and alkoxy; a group of the formula -CH₂CN; a group of the formula -CH₂CO₂R', wherein R' represents hydrogen

or an alkyl group; a group of the formula $-\text{CH}_2\text{CONR}^{\text{IV}}\text{R}^{\text{V}}$, wherein R^{IV} and R^{V} independently represents hydrogen or an alkyl group; or a group of the formula $-\text{CH}_2\text{C}(=\text{NOH})\text{NH}_2$;

R^2 represents hydrogen, an alkyl group, a cycloalkyl group, a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, alkyl, cycloalkyl, hydroxy, and alkoxy; and

R^3 , R^4 and R^5 independently of each another represents hydrogen; halogen; $-\text{NO}_2$; $-\text{CN}$; $-\text{CF}_3$; an alkyl group; an alkoxy group; a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, alkyl, cycloalkyl, hydroxy, and alkoxy; or a group of the formula $-\text{SO}_2\text{NR}''\text{R}'''$, wherein R'' and R''' independently of each another represents hydrogen or an alkyl group;

or R^5 is as defined above and R^3 and R^4 together form an additional 4 to 7 membered fused ring, which fused ring may be a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or a group of the formula $-\text{SO}_2\text{NR}''\text{R}'''$, wherein R'' and R''' independently of each another represents hydrogen or an alkyl group.

In a preferred embodiment, R^1 represents hydrogen or an alkyl group.

In another preferred embodiment, R^2 represents hydrogen or an alkyl group.

In a third preferred embodiment, R^3 , R^4 and R^5 independently of each another represents hydrogen or an alkyl group.

In a most preferred embodiment, the compound of the invention is

1-Ethyl-4,5-dichlorobenzimidazolone;

1,3-diethyl-4,5-dichlorobenzimidazolone; or

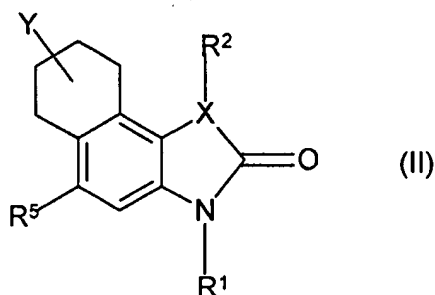
3-Ethyl-5-chlorobenzoxazolone;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

In another preferred embodiment, R^3 and R^4 together form a 5- or 6-membered fused ring, which fused ring may be a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of

halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or a group of the formula $-\text{SO}_2\text{NR}''\text{R}'''$, wherein R'' and R''' independently of each another represents hydrogen or an alkyl group.

In a yet more preferred embodiment, chemical compound of the invention may be represented by the general formula



5

wherein R^1 , R^2 , R^5 and X are as defined above; and

Y represents hydrogen, halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or a group of the formula $-\text{SO}_2\text{NR}''\text{R}'''$, wherein R'' and R''' independently of each another represents hydrogen or an alkyl group.

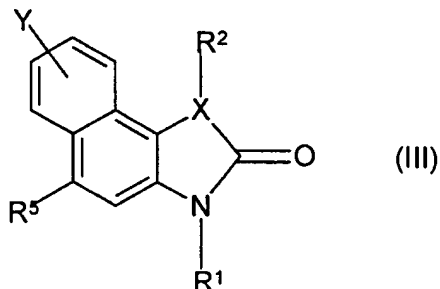
10 In a preferred embodiment the compound of the invention is a chemical compound of formula II, wherein R^1 represents hydrogen or an alkyl group.

In another preferred embodiment the compound of the invention is a chemical compound of formula II, wherein R^2 represents hydrogen or an alkyl group.

In a third preferred embodiment the compound of the invention is a
15 chemical compound of formula II, wherein Y represents hydrogen.

In a most preferred embodiment, the chemical compound of the invention is 1,3-diethyl-5,6,7,8-tetrahydronaphtho[1,2-d]imidazolinone; or 1-ethyl-5,6,7,8-tetrahydronaphtho[1,2-d]imidazolinone; or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

20 In another preferred embodiment, the chemical compound of the invention may be represented by the general formula



wherein R¹, R², R⁵ and X are as defined above; and

Y represents hydrogen, halogen, -NO₂, -CN, -CF₃, or a group of the formula -SO₂NR''R''', wherein R'' and R''' independently of each another represents hydrogen or an alkyl group.

5 In a preferred embodiment the compound of the invention is a chemical compound of formula III, wherein R¹ represents hydrogen or an alkyl group.

In another preferred embodiment the compound of the invention is a chemical compound of formula III, wherein R² represents hydrogen or an alkyl group.

In a third preferred embodiment the compound of the invention is a
10 chemical compound of formula III, wherein Y represents hydrogen.

In a most preferred embodiment, the chemical compound of the invention is 3-Ethyl-naphto[1,2-d]oxazolinone; 3-Ethyl-naphto[1,2-d]imidazolinone; or 3-Ethyl-quinolino[5,6-d]imidazolinone; or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

15 In yet another preferred embodiment, the chemical compound of the invention is represented by formula I, in which R³ and R⁴ together form a 5-membered heterocyclic fused ring, which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halogen, -NO₂, -CN, -CF₃. In a more preferred embodiment, the heterocyclic ring is a 1,2 or 4-imidazolyl, 20 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, 2 or 3-thienyl.

In a most preferred embodiment, the chemical compound is 3-Benzyl-(2,1,3-thiadiazolo)[4,5-g]benzimidazolone, or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

25 Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or a iodine atom.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain
30 preferably contain of from one to twelve carbon atoms (C₁₋₁₂-alkyl), more preferred of from one to six carbon atoms (C₁₋₆-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C₁₋₄-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary

butyl. In a most preferred embodiment alkyl represents a C₁₋₃-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C₃₋₇-cycloalkyl),
5 including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above.

In the context of this invention an acyl group designates a carboxy group or an alkylcarbonyl group, wherein alkyl is as defined above. Examples of preferred
10 acyl groups of the invention are carboxy, acetyl, and propionyl.

In the context of this invention a heterocyclic group is a cyclic group, which holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). One or more of the ring structures may in particular be aromatic (i.e. a heteroaryl), saturated or partially saturated.
15 Preferred heterocyclic monocyclic groups of the invention include 5- and 6 membered heterocyclic monocyclic groups.

Examples of preferred aromatic heterocyclic monocyclic groups of the invention include 1,3,2,4- or 1,3,4,5-dioxadiazolyl, dioxatriazinyl, dioxazinyl, 1,2,3-, 1,2,4-, 1,3,2- or 1,3,4-dioxazolyl, 1,3,2,4- or 1,3,4,5-dithiadiazolyl, dithiatrizinyl,
20 dithiazinyl, 1,2,3-dithiazolyl, 2- or 3-furanyl, furazanyl, 1,2 or 4-imidazolyl, isoindazolyl, isothiazol-3,4 or 5-yl, isoxazol-3,4 or 5-yl, 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4-oxadiazol-3,4 or 5-yl, oxatetrazinyl, oxatriazinyl, 1,2,3,4- or 1,2,3,5-oxatriazolyl, oxazol-2,4 or 5-yl, 2 or 3-pyrazinyl, 1,3 or 4-pyrazolyl, 3 or 4-pyridazinyl, 2,3 or 4-pyridinyl, 2,4 or 5-pyrimidinyl, 1,2 or 3-pyrrolyl (azolyl), 1,2,3,4- or 2,1,3,4-tetrazolyl,
25 thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, 2 or 3-thienyl, 1,2,3-, 1,2,4- or 1,3,5-triazinyl, and 1,2,3-, 1,2,4-, 2,1,3- or 4,1,2-triazolyl. Most preferred heterocyclic groups are 1,2 or 4-imidazolyl, 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, and 2 or 3-thienyl.

Examples of preferred saturated or partially saturated heterocyclic
30 monocyclic groups of the invention include 1,3,5,6,2-dioxadiazinyl, 1,2,3,4,5-, 1,2,3,5,4-dioxadiazolyl, dioxanyl, 1,3-dioxolyl, 1,3,5,6,2-dithiadiazinyl, 1,2,3,4,5- or 1,2,3,5,4-dithiadiazolyl, 2-isoimidazolyl, isopyrrolyl, isotetrazolyl, 1,2,3- or 1,2,4-isotriazolyl, morpholinyl, oxadiazinyl, 1,2,4-, 1,2,6-, 1,3,2-, 1,3,6- or 1,4,2-oxazinyl,

piperaziny, homopiperaziny, piperidiny, 1,2-, 1,3- or 1,4-pyrany, and 1,2,3-pyrrolidiny.

Pharmaceutically Acceptable Salts

5 The SK/IK/BK channel modulating agents of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

 Examples of pharmaceutically acceptable addition salts include, without
10 limitation, the non-toxic inorganic and organic acid addition salts such as the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzenesulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the
15 enantate derived from enanthic acid, the formate derived from formic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the
20 mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the
25 stearate derived from stearic acid, the succinate derived from succinic acid, the sulphate derived from sulphuric acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

 Other acids such as oxalic acid, which may not be considered
30 pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

The chemical compound of the invention may be provided in unsolved or
5 solvated forms together with a pharmaceutically acceptable solvents such as water, ethanol, and the like. Solvated forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, solvated forms are considered equivalent to unsolved forms for the purposes of this invention.

10

Steric Isomers

The SK/IK/BK channel modulating agents of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

15

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic
20 compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the
25 present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the
30 art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Biological Activity

According to the present invention it has now been found that the isatin derivatives of the invention possess valuable activity as modulators of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.

5 The SK/IK/BK channel modulating activity may be monitored using conventional electrophysiological methods such as patch-clamp techniques, or conventional spectroscopic methods such as FLIPR assay (Fluorescence Image Plate Reader; available from Molecular Devices). These methods generally comprises subjecting an SK_{Ca}, IK_{Ca} or BK_{Ca} containing cell to the action of the chemical
10 compound of the invention, followed by monitoring the membrane potential of the SK_{Ca}, IK_{Ca} or BK_{Ca} containing cell in order to identify changes in the membrane potential caused by the action of the compound of the invention.

In Example 6 the biological activity of the compounds of the invention is demonstrated using electrophysiologic patch-clamp techniques.

15 Based on their biological activity the compounds of the invention are considered useful for the treatment or alleviation of diseases or conditions responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK channels, including diseases or conditions like respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal
20 disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea,
25 narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

The compounds of the invention is considered particularly useful for
30 reducing or inhibiting undesired immunoregulatory actions. In a preferred embodiment, therefore, the compounds of the may be used in the treatment or alleviation of a diseases, disorders or condition related to immune dysfunction, or in order to obtain immune suppression in an individual in need herefore.

In another, and still more preferred embodiment, the invention relates to the use of a compound of the invention in a combination therapy with known immune-suppressants for the treatment or alleviation of a diseases, disorders or condition related to immune dysfunction, or for obtaining immune suppression. Preferred
5 immune-suppressants to combine with the compounds of the invention include the calcineurin inhibitors (i.e. protein phosphatase 2B inhibitors), in particular Cyclosporin, and FK506.

Conditions which may benefit from this treatment include, but are not limited to diseases, disorders or conditions such as autoimmune diseases, e.g.
10 Addison's disease, alopecia areata, Ankylosing spondylitis, haemolytic anemia (anemia haemolytica), pernicious anemia (anemia perniciosa), aphthae, aphthous stomatitis, arthritis, arteriosclerotic disorders, osteoarthritis, rheumatoid arthritis, aspermiogenese, asthma bronchiale, autoimmune asthma, autoimmune haemolysis, Bechet's disease, Boeck's disease, inflammatory bowel disease, Burkitt's lymphoma,
15 Chron's disease, chorioiditis, colitis ulcerosa, Coeliac disease, cryoglobulinemia, dermatitis herpetiformis, dermatomyositis, insulin-dependent type I diabetes, juvenile diabetes, idiopathic diabetes insipidus, insulin-dependent diabetes mellis, autoimmune demyelinating diseases, Dupuytren's contracture, encephalomyelitis, encephalomyelitis allergica, endophthalmia phacoanaphylactica, enteritis allergica,
20 autoimmune enteropathy syndrome, erythema nodosum leprosum, idiopathic facial paralysis, chronic fatigue syndrome, febris rheumatica, glomerulo nephritis, Goodpasture's syndrome, Graves' disease, Hamman-Rich's disease, Hashimoto's disease, Hashimoto's thyroiditis, sudden hearing loss, sensoneural hearing loss, hepatitis chronica, Hodgkin's disease, haemoglobinuria paroxysmatica,
25 hypogonadism, ileitis regionalis, iritis, leucopenia, leucemia, lupus erythematosus disseminatus, systemic lupus erythematosus, cutaneous lupus erythematosus, lymphogranuloma malignum, mononucleosis infectiosa, myasthenia gravis, traverse myelitis, primary idiopathic myxedema, nephrosis, ophthalmia symphatica, orchitis granulomatosa, pancreatitis, pemphigus, pemphigus vulgaris, polyarteritis nodosa,
30 polyarthritis chronica primaria, polymyositis, polyradiculitis acuta, psoreasis, purpura, pyoderma gangrenosum, Quervain's thyreoiditis, Reiter's syndrome, sarcoidosis, ataxic sclerosis, progressive systemic sclerosis, scleritis, sclerodermia, multiple sclerosis, sclerosis disseminata, acquired spenic atrophy, infertility due to antispermatozoan antibodies, thrombocytopenia, idiopathic thrombocytopenia

purpura, thymoma, acute anterior uveitis, vitiligo, AIDS, HIV, SCID and Epstein Barr virus associated diseases such as Sjorgren's syndrome, virus (AIDS or EBV) associated B cell lymphoma, parasitic diseases such as Leishmania, and immunosuppressed disease states such as viral infections following allograft
5 transplantations, graft vs. Host syndrome, transplant rejection, or AIDS, cancers, chronic active hepatitis diabetes, toxic shock syndrome, food poisoning, and transplant rejection.

Pharmaceutical Compositions

10 In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a chemical compound having SK_{Ca}, IK_{Ca} or BK_{Ca} modulating activity.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce
15 the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the SK/IK/BK channel modulating agents of the invention, or
20 a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients, known and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

25 Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, and intravenous injection) administration, or those in a form suitable for administration by inhalation or insufflation.

30 The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the

same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may
5 contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either
10 a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets,
15 suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the
20 finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about
25 seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the
30 active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

- 5 Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection
10 liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled
15 syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by
20 lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

- 25 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be
30 converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be
5 formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia
10 or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions
15 may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an
20 aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

25 Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in
30 capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle

size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

5 The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage
10 form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be
15 found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50} , may be determined by standard pharmacological procedures in cell
20 cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50} . Pharmaceutical compositions which exhibit large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of
25 administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired
30 therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment or alleviation of diseases or disorders or conditions of living animals, including humans, which diseases, disorders or conditions are responsive to modulation of SK_{Ca} , IK_{Ca} and/or BK_{Ca} channels, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a chemical compound of the invention.

In a more preferred embodiment, the disease, disorder or condition is asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

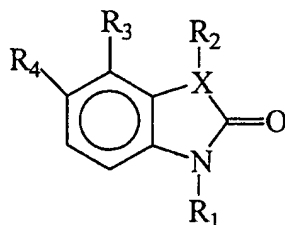
It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

EXAMPLES

The invention is further illustrated with reference to the following examples which are not intended to be in any way limiting to the scope of the invention as claimed.

Table 1

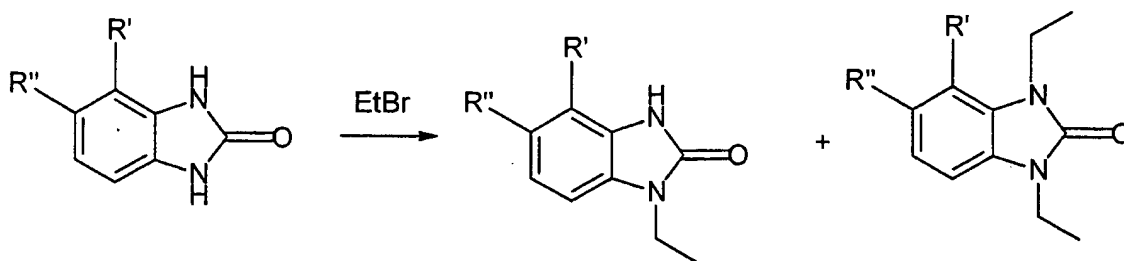
Substituted, fused Imidazolinones and Oxazolinones



Entry	X	R ₁	R ₂	R ₃	R ₄	Mp.	Examples
1a	N	Et	Et	-(CH ₂) ₄ -		oil	1, 2, 3
1b	N	Et	H	-(CH ₂) ₄ -		171-4	1, 2, 3
1c	O	Et	-	-CH=CH-CH=CH-		137.7-138.4	1, 2, 4
1d	N	Et	H	-CH=CH-CH=CH-		240-242	1, 2a, 4
1e	N	Bz	H	=N-S-N=		245-247	2a, 5
1f	N	Et	H	-N=CH-CH=CH-		258-259	1, 2
1g	N	Et	H	Cl	Cl	186-8	1, 2a, 4
1h	N	Et	Et	Cl	Cl	oil	1, 2a, 4
1i	O	H	-	H	Cl	-	-
1j	O	Et	-	H	Cl	75-78	1a

10

Example 1



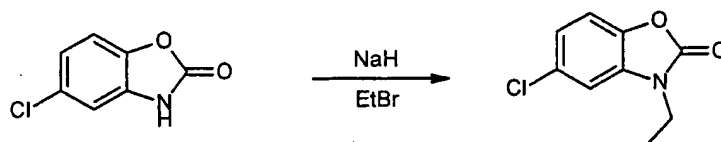
1-Ethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone (**1b**) and 1,3-diethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone (**1a**). To a solution of 5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone (1.0 g; 5.7 mmol) in anhydrous DMF (10 ml) was added sodium hydride (4.5 mmol; 0.18 g, 60% dispersion in mineral oil). When the evolution of hydrogen had ceased bromoethane (0.34 ml; 4.5 mmol) was added and the mixture was stirred at ambient temperature overnight. The mixture was poured into water and extracted with ethyl acetate. The extract was concentrated and the resulting product mixture was separated by column-chromatography on silica gel using a mixture of ethyl acetate and ligroin (1:4 v/v) as the eluent. Yield of 1-Ethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone: 0.12 g. Mp. 171-174°C. Yield (isolated as an oil) of 1,3-diethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone: 0.12 g, m/z: 244 (100%), 229 (31%), 216 (33%), 215 (22%), 188 (13%).

3-Ethyl-naphto[1,2-d]oxazolinone (**1c**) was prepared analogously by treatment of naphto[1,2-d]oxazolinone with sodium hydride (1.1 eq.) and bromoethane (1.1 eq.), successively. Yield after column-chromatographic workup: 14%. Mp. 137.7-138.4°C.

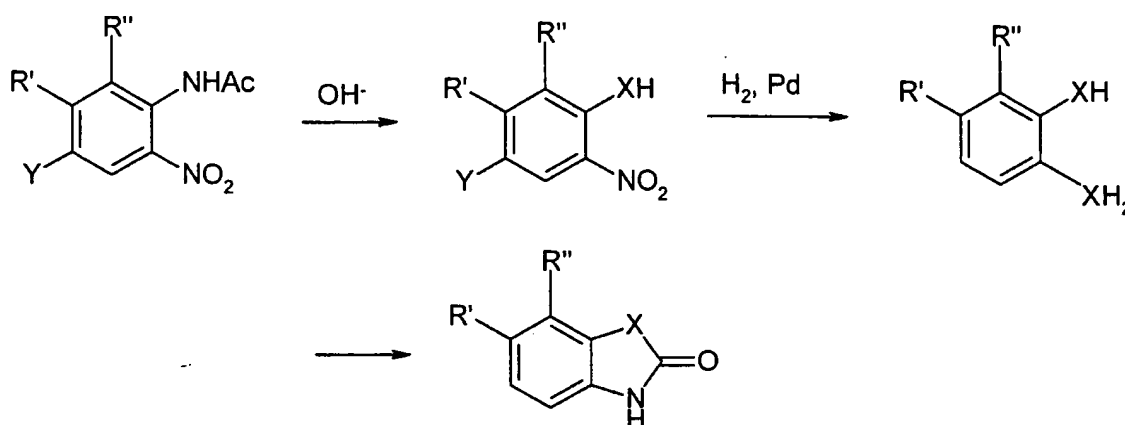
3-Ethyl-naphto[1,2-d]imidazolinone (**1d**) was prepared analogously by treatment of naphto[1,2-d]imidazolinone with sodium hydride (1.1 eq.) and bromoethane (1.1 eq.), successively. Yield after column-chromatographic workup: 2%. Mp. 240-242°C.

3-Ethyl-quinolino[5,6-d]imidazolinone (**1f**) was prepared analogously by treatment of quinolino[5,6-d]imidazolinone with sodium hydride (1.1 eq.) and bromoethane (1.1 eq.), successively. Yield after column-chromatographic workup: 12%. Mp. 258-259°C.

1-Ethyl-4,5-dichlorobenzimidazolone (**1g**) and 1,3-diethyl-4,5-dichlorobenzimidazolone (**1h**) were prepared analogously by treatment of 4,5-dichlorobenzimidazolone with sodium hydride (1.1eq) and bromoethane (1.1eq) successively. The products were separated by column-chromatography. Yield of **1g**: 26%. Mp. 186-188°C. Yield of **1h**: 16%. Oil.

Example 1a

3-Ethyl-5-chlorobenzoxazolone (1j) was prepared as described in Example 1 by treatment of chloroxazolone (1i) with sodium hydride (1.1 eq.) and bromoethane (1.1 eq.), successively. Yield: 47%. Mp. 75-78°C

Example 2

X = NH or O; Y = H or Br

10

1,2-Diamino-5,6,7,8-tetrahydronaphthalene (2a). 1-(Acetylamino)-2-nitro-5,6,7,8-tetrahydronaphthalene (2.5 g; 10.7 mmol) was suspended in a mixture of dimethoxyethane (30 ml) and aqueous sodium hydroxide (32 ml, 1 M). The mixture was heated to reflux for 2 hours. After cooling two volumes of ice-water was added, and the mixture was neutralised by addition of hydrochloric acid (32 ml, 1 M). The product was filtered off, washed with water and air-dried to yield 1-amino-2-nitro-5,6,7,8-tetrahydronaphthalene (1.95 g, 95%). This product (1.92 g; 10.0 mmol) was dissolved in ethanol and hydrogenated at ambient pressure using Pd (5% on activated carbon) as the catalyst. When the hydrogen uptake had ceased, the mixture was filtered through celite and the filtrate was evaporated to dryness to leave 1,2-diamino-5,6,7,8-tetrahydronaphthalene (1.55 g, 96%).

1,2-Diaminonaphtalene (**2b**) was prepared analogously from 1-(acetylamino)-4-bromo-2-nitronaphtalene (Example 4).

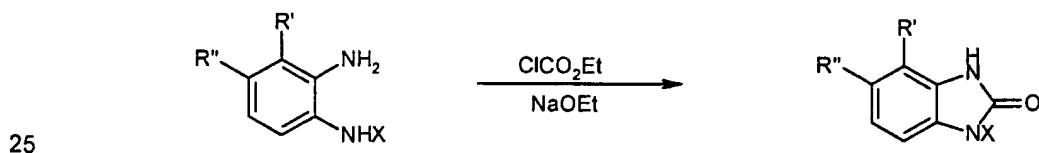
- 5 3,4-Dichlorophenylenediamine (**2c**) was prepared analogously from 2,3-dichloro-4-bromo-6-nitro acetanilide (Example 4)

5,6,7,8-Tetrahydronaphto[1,2-d]imidazolinone (**2d**). To a solution of 1,2-diamino-5,6,7,8-tetrahydronaphtalene (1.5 g; 9.3 mmol) in diglyme (40 ml) was added urea (0.73; 12.04 mmol) and the mixture was heated to 160°C for 2 hours. After cooling the mixture was poured into ice-water. The product was filtered off, washed with water and dried. Quantitative yield.

Naphto[1,2-d]oxazolinone (**2e**). When 1-(acetylamino)-4-bromo-2-nitronaphtalene was treated with aqueous sodium hydroxide as described above the product was 4-bromo-2-nitro-1-naphtol - i.e. substitution occurred instead of hydrolysis. Subsequent hydrogenation and treatment with urea yielded naphto[1,2-d]oxazoline in 44% overall yield.

- 20 Quinolino[5,6-d]imidazolinone (**2f**) was prepared from 5-amino-6-nitroquinoline by hydrogenation and subsequent treatment with urea in diglyme. Overall yield: 91%.

Example 2a



Naphto[1,2-d]imidazolinone (**2g**). To a solution of 1,2-diaminonaphtalene (6.3 g, 39.9 mmol) and triethylamine (18 ml, 128 mmol) in anhydrous THF (50 ml) was added ethyl chloroformate (11.5 ml, 120 mmol) over 10 min. The reaction mixture was heated to reflux for 1.5 hours. The solvent was removed by evaporation and the residue was partitioned between water and ethyl acetate. The organic phase was concentrated under reduced pressure, and the residue was redissolved in abs. ethanol (50 ml). A solution of sodium ethanolate in ethanol (8 ml, 2 M) was added and the mixture was

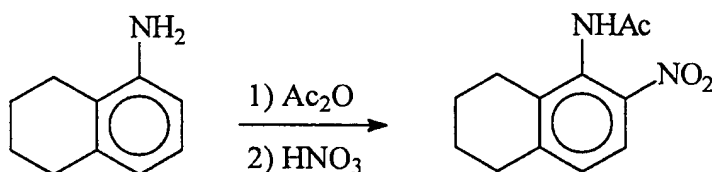
heated to reflux overnight. The product precipitated quantitatively upon concentration of the reaction mixture.

3-Benzyl-(2,1,3-thiadiazolo)[4,5-g]benzimidazolone (**1e**) was prepared analogously from 4-amino-5-(benzylamino)benzo-2,1,3-thiadiazole (Example 5). The product was triturated with dichloromethane. Yield: 21%. Mp. 245-247°C.

4,5-Dichlorobenzimidazolone (**2h**) was prepared analogously from 3,4-phenylenediamine (Example 4)

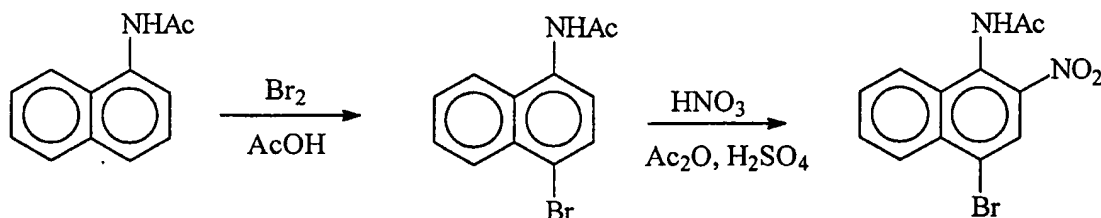
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Example 3



1-(Acetylamino)-2-nitro-5,6,7,8-tetrahydronaphthalene (**3a**). A suspension of 1-amino-5,6,7,8-tetrahydronaphthalene (5 ml; 30 mmol) in acetic anhydride (75 ml) was stirred at ambient temperature for 30 min. After cooling to 15°C nitric acid (1.5 ml, 65%) was added and the mixture was allowed to warm to room temperature. Stirring was continued overnight. The mixture was poured into ice-water and the oily precipitate was filtered off, washed with water and dried. This crude product was purified by column-chromatography on silica gel, using a mixture of ethyl acetate and ligroin (1:1) as the eluent. Yield: 2.5 g (30%).

Example 4



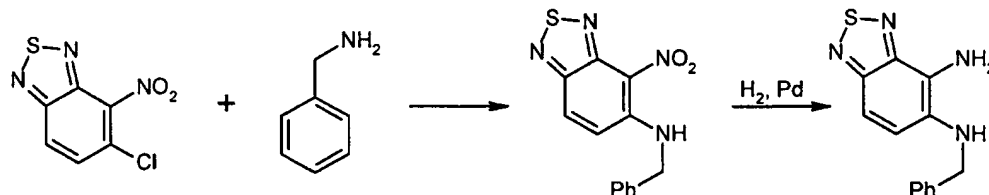
25

1-(Acetylamino)-4-bromo-2-nitronaphtalene (**4a**). To a suspension of 1-(acetylamino)naphtalene (42 g; 0.23 mol) in glacial acetic acid (400 ml) was added a solution of bromine (12.8 ml; 0.25 mol) in glacial acetic acid (50 ml) over 30 min. The resulting suspension was stirred at ambient temperature for 3.5 hours. The mixture was poured into water and the product was filtered off, washed with water and dried. Yield: 60 g (100%) of 1-(acetylamino)-4-bromonaphtalene.

This product (60 g; 0.23 mmol) was suspended in acetic anhydride (600 ml) and cooled in an ice-bath. Concentrated sulphuric acid (10 ml) was added followed by dropwise addition of a cold solution of nitric acid (9.5 ml, 65%) in acetic anhydride (100 ml) to the vigorously stirred suspension at 10-15°C. At the end of the addition (1.5 hours) the mixture was stirred for additionally 1 hour. The resulting mixture was poured into ice-water (1 l) and the product was filtered off, washed with water and dried. Recrystallisation from abs. ethanol (1.3 l) afforded 1-(acetylamino)-4-bromo-2-nitronaphtalene (29.1 g, 41%).

2,3-Dichloro-4-bromo-6-nitro acetanilide (**4b**) was prepared analogously from 2,3-dichloroaniline.

Example 5



4-amino-5-(benzylamino)benzo-2,1,3-thiadiazole (**5a**). To a solution of 5-chloro-4-nitro-2,1,3-thiadiazole (1.0 g, 4.64 mmol) in anhydrous NMP (5 ml) was added triethylamine (0.65ml, 4.64mmol) and benzylamine (0.51 ml, 4.64 mmol). The mixture was heated to 80°C for 1 hour. The cooled mixture was poured into ice-water (50 ml) and the product was filtered off, washed with water and dried. Yield: 1g (75%). This product (0.5 g, 1.75 mmol) was suspended in ethanol (20 ml) and hydrogenated at ambient pressure using palladium (5% on activated carbon) as the catalyst. Yield: quantitative.

Example 6

Electrophysiological Experiments

In this example, the biological activity of the compounds of the invention is demonstrated using electrophysiologic patch-clamp techniques.

Intermediate-conductance Ca^{2+} -activated K^{+} channels (IK channels) have been cloned from human placenta and stably expressed in HEK293 cells. The ionic current through the channels is recorded in the whole-cell mode of the patch-clamp technique.

10

Stable Expression of IK in HEK293 Cells

Human IK (hIK) was excised from pT3T7 (GenBank Acc. No. N56819) using EcoR I and Not I, and subcloned into the mammalian expression vector pNS1Z (NeuroSearch), a custom designed derivative of pcDNA3Zeo (Invitrogen), to give the plasmid construct pNS1Z_hIK.

HEK293 tissue culture cells were grown in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% FCS (foetal calf serum) at 37°C in 5% CO_2 . One day prior to transfection, 10^6 cells were plated in a cell culture T25 flask. The following day, cells were transfected using lipofection (20 μL Lipofectamin™, Life Technologies, with 2.5 μg of the plasmid pNS1Z_hIK in a total volume of 540 μL).

The lipofection mixture was overlaid on the cells and incubated at 37°C for 5 hours. The cells were then rinsed with regular media and grown for 72 hours in DMEM, 10% FCS at 37°C in 5% CO_2 .

72 hours post transfection, cells transfected with pNS1Z_hIK were selected in media supplemented with 0.25mg/ml Zeocin. Single clones were picked and propagated in selection media until sufficient cells for freezing were available. Hereafter the cells were cultured in regular medium without selection agent.

Expression of functional hIK channels was verified by patch-clamp measurements.

30

Whole Cell Recordings

Experiments are carried out on one of several patch-clamp set-ups. Cells plated on coverslips are placed in a 15 μL perfusion chamber (flowrate ~1 ml/min) mounted on a IMT-2 microscope equipped with Nomarski or Hoffmann optics. The

microscopes are placed on vibration-free tables in grounded Faraday cages. All experiments are performed at room temperature (20 - 22°C). EPC-9 patch-clamp amplifiers (HEKA-electronics, Lambrect, Germany) are connected to Macintosh computers via ITC16 interfaces. Data are stored directly on the hard disk and
5 analysed by the IGOR software (WaveMetrics, Lake Oswega, USA).

The whole-cell configuration of the patch clamp technique is applied. The tip of a borosilicate pipette (resistance 2-4 M Ω) is gently (remote control system) placed on the cell membrane. Light suction results in a giga seal (pipette resistance increases to more than 1 G Ω) and the cell membrane is then ruptured by more
10 powerful suction. Cell capacitance is electronically compensated and the resistance between the pipette and the cell interior (the series resistance, R_s) is measured and compensated for. Usually the cell capacitance ranges from 5 to 20 pF (depending on cell size) and the series resistance is in the range 3 to 6 M Ω . R_s - as well as capacitance compensation are updated during the experiments (before each
15 stimulus).

All experiments with drifting R_s -values are discharged. Leak-subtractions are not performed.

Solutions

20 All compounds described in Table 1 were subjected to this experiment.

The extracellular (bath) solution contains: 144 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES (pH = 7.4). Test compounds are dissolved in DMSO from stock solution and then diluted to a final concentration of about 10 μ M in the extracellular solution. The concentration of CaCl₂ is 7.6 mM and that of MgCl₂ is 1.2 mM to give
25 calculated free concentrations of 300 nM and 1 mM, respectively.

Quantification

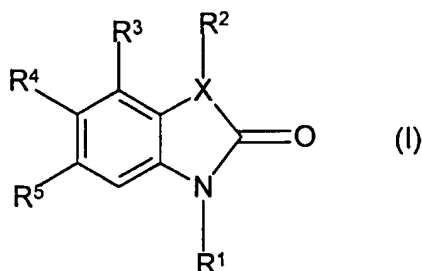
After establishment of the whole-cell configuration, voltage-ramps (usually -100 to +100 mV) are applied to the cell every 5 sec. A stable baseline current is
30 obtained within a period of 100-300 seconds, and the compounds are then added by changing to an extracellular solution containing the compound to be tested. Very little endogen current (<200 pA at 100 mV, compared to 2-20 nA IK current) are activated under these circumstances in native HEK293 cells.

Results

All compounds tested in this experiment showed activity at a final concentration of about 10 μ M, and these compounds therefore are SK/IK/BK channel modulating agents.

CLAIMS

1. A chemical compound represented by the general formula



- 5 or a pharmaceutically acceptable salt or an oxide or a hydrate thereof,
wherein,

X represents N, O, or S; and

- 10 R^1 represents hydrogen; an alkyl group; a cycloalkyl group; hydroxy; an alkoxy group; an acyl group; a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, $-NO_2$, $-CN$, $-CF_3$, alkyl, cycloalkyl, hydroxy, and alkoxy; a group of the formula $-CH_2CN$; a group of the formula $-CH_2CO_2R'$, wherein R' represents
15 hydrogen or an alkyl group; a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V independently represents hydrogen or an alkyl group; or a group of the formula $-CH_2C(=NOH)NH_2$;

- R^2 represents hydrogen, an alkyl group, a cycloalkyl group, a phenyl or a
20 benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, $-NO_2$, $-CN$, $-CF_3$, alkyl, cycloalkyl, hydroxy, and alkoxy; and

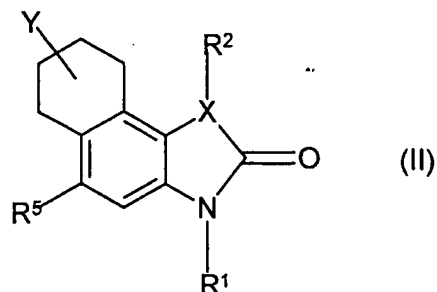
- R^3 , R^4 and R^5 independently of each another represents hydrogen;
25 halogen; $-NO_2$; $-CN$; $-CF_3$; an alkyl group; an alkoxy group; a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halogen, $-NO_2$, $-CN$, $-CF_3$, alkyl, cycloalkyl,

hydroxy, and alkoxy; or a group of the formula $-\text{SO}_2\text{NR}''\text{R}'''$, wherein R'' and R''' independently of each another represents hydrogen or an alkyl group;

5 or R^5 is as defined above and R^3 and R^4 together form an additional 4 to 7
membered fused ring, which fused ring may be a heterocyclic ring, it may be an
aromatic, saturated or partially saturated ring, and which fused ring may
optionally be substituted one or more times with substituents selected from the
group consisting of halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or a group of the formula $-\text{SO}_2\text{NR}''\text{R}'''$, wherein R'' and R''' independently of each another represents
10 hydrogen or an alkyl group.

2. The chemical compound according to claim 1, wherein R^1 represents hydrogen or an alkyl group.
- 15 3. The chemical compound according to either of claims 1-2, wherein R^2 represents hydrogen or an alkyl group.
4. The chemical compound according to any of claims 1-3, wherein R^3 , R^4 and R^5 independently of each another represents hydrogen or an alkyl group.
- 20 5. The chemical compound according to claim 1 which is
1-Ethyl-4,5-dichlorobenzimidazolone;
1,3-diethyl-4,5-dichlorobenzimidazolone; or
3-Ethyl-5-chlorobenzoxazolone;
25 or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.
6. The chemical compound according to any of claims 1-3, wherein R^3 and R^4 together form a 5- or 6-membered fused ring, which fused ring may be a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and
30 which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, or a group of the formula $-\text{SO}_2\text{NR}''\text{R}'''$, wherein R'' and R''' independently of each another represents hydrogen or an alkyl group.

7. The chemical compound according to Claim 6, which is represented by the general formula



or a pharmaceutically acceptable salt or an oxide or a hydrate thereof,
wherein,

X, R¹, R² and R⁵ are as defined above; and

Y represents hydrogen, halogen, -NO₂, -CN, -CF₃, or a group of the
formula -SO₂NR''R''', wherein R'' and R''' independently of each another
represents hydrogen or an alkyl group.

8. The chemical compound according to claim 7, wherein R¹ represents hydrogen or an alkyl group.

9. The chemical compound according to either of claims 7-8, wherein R² represents hydrogen or an alkyl group.

10. The chemical compound according to any of claims 7-9, wherein Y represents hydrogen.

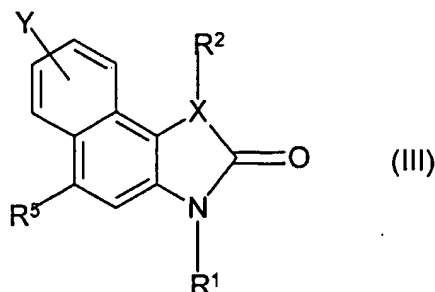
11. The chemical compound according to claim 7, which is

1,3-diethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone; or

1-ethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

12. The chemical compound according to claim 6, which is represented by the general formula



or a pharmaceutically acceptable salt or an oxide or a hydrate thereof,
wherein,

5

X, R¹, R² and R⁵ are as defined above; and

Y represents hydrogen, halogen, -NO₂, -CN, -CF₃, or a group of the
formula -SO₂NR''R''', wherein R'' and R''' independently of each another
represents hydrogen or an alkyl group.

10

13. The chemical compound according to claim 12, wherein R¹ represents hydrogen
or an alkyl group.

14. The chemical compound according to either of claims 12-13, wherein R²
represents hydrogen or an alkyl group.

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15. The chemical compound according to any of claims 12-14, wherein Y represents
hydrogen.

20

16. The chemical compound according to claim 12, wherein the chemical compound
is

3-Ethyl-naphto[1,2-d]oxazolinone;

3-Ethyl-naphto[1,2-d]imidazolinone; or

3-Ethyl-quinolino[5,6-d]imidazolinone;

25

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

17. The chemical compound according to claim 6, in which R³ and R⁴ together form a 5-membered heterocyclic fused ring, which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halogen, -NO₂, -CN, -CF₃.
18. The chemical compound according to claim 17, in which the heterocyclic ring is a 1,2 or 4-imidazolyl, 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, or 2 or 3-thienyl.
19. The chemical compound according to claim 18, which is
3-Benzyl-(2,1,3-thiadiazolo)[4,5-g]benzimidazolone;
or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.
20. A pharmaceutical composition comprising a therapeutically-effective amount of a chemical compound of claims 1-19, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for the treatment or alleviation of a disease or a disorder or a condition responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.
21. The pharmaceutical composition according to claim 20, for the treatment or alleviation of respiratory diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

22. Use of a chemical compound according to any of claims 1-19 for the manufacture of a pharmaceutical composition for the treatment or alleviation of a disorder or a disease or a condition of a mammal, including a human, which disorder, disease or condition is responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels.
23. The use according to claim 22, wherein the disease, disorder or condition is asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence-seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.
24. A method of treatment or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK_{Ca} channels, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound according to any of claims 1-19.
25. The method of claim 24, in which the disease, disorder or condition is asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic hearth disease, angina

pectoris, coronary hearth disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, and immune suppression.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 99/00681

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D235/26 C07D263/60 C07D277/68 A61K31/4184 A61K31/423
A61K31/429 A61P9/00 A61P11/08 A61P13/10 A61P13/12
A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CA EPO-Internal CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
4 X	EP 0 477 819 A (NEUROSEARCH AS) 1 April 1992 (1992-04-01) the whole document	1-25
5 X	EP 0 545 845 A (NEUROSEARCH AS) 9 June 1993 (1993-06-09) the whole document	1-25

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

20 March 2000

Date of mailing of the international search report

25. 04. 2000

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Eva Johansson

INTERNATIONAL SEARCH REPORT

International Application No
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17	X CHEMICAL ABSTRACTS, vol. 64, no. 13, 20 June 1966 (1966-06-20) Columbus, Ohio, US; abstract no. 19585g, TOYOSHIMA S ET AL: "Synthesis of benzoxazoline and benzoxazinone derivatives. I." XP002900923 abstract & YAKUGAKU ZASSHI, vol. 86, no. 3, 1966, pages 203-209, A	1-5,20, 21 6-19, 22-25
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Int ernational Application No

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 99/00681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
19	<p>X</p> <p>DATABASE STN INTERNATIONAL [Online]</p> <p>KADYROV CH SH ET AL: "Study of the correlation between herbicide activity and chemical structure of some benzimidazole derivatives"</p> <p>retrieved from CAPLUS, accession no. 1975:602657</p> <p>Database accession no. 83:202657</p> <p>XP002900928</p> <p>abstract</p> <p>& FIZIOL. RAST.,</p> <p>vol. 21, no. 6, 1974, pages 1276-1281,</p> <p>-----</p>	1-3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **24, 25**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00681

Claims 24, 25 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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INTERNATIONAL SEARCH REPORT

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INTERNATIONAL SEARCH REPORT

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